Chapter 5

Indicators for human toxicity in Life Cycle Impact Assessment

Position paper for SETAC-Europe WIA2 Task Group on Human toxicity
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Abstract

The main objectives of this task group under SETAC-Europe's Second Working Group on Life Cycle Impact Assessment (LCIA-WIA2) were to identify and discuss the suitability of toxicological impact measures for human health for use in characterization in LCIA. The current state of the art of defining health indicators in LCIA is summarized in this document, promising approaches are addressed in further detail under the two headings of potency and severity, and then the suitability of the approaches is discussed with the aid of selected criteria. Toxicological potency factors are based on test data such as No Observed Effect Levels (NOEL). NOELs, and similar data, are determined in laboratory studies using rodents and are then extrapolated to more relevant human measures. Many examples also exist of measures and methods beyond potency-based indicators that attempt to account for differences in expected severity, as well as potency. Quantitative severity-based indicators yield measures in terms of Years of Life Lost (YOLL), Disability Adjusted Life Years (DALY), Quality Adjusted Life Years (QALY) and other similar measures. DALYs and QALYs are examples of approaches that attempt to account for both years of life lost (mortality) and years of impaired life (morbidity). Qualitative severity approaches tend to arrange potency-based indicators in categories, avoiding the need to quantitatively express differences in severity. Based on the proposed criteria and current state of the knowledge, toxicological potency indicators are pre-selected as a minimum default. Addressing accuracy and ensuring consistency, particularly when extrapolating data, are seen as some of the key issues that are beginning to be addressed in LCIA. While associated approaches are still in their infancy, it is encouraged to take into account relative severity whenever possible using qualitative and/or quantitative approaches.

1. Introduction

This position paper was prepared by the Task Group on Human Toxicity, which was established under the SETAC Europe's Second Working Group on Life Cycle Impact Assessment (WIA2). The objective of WIA2 is 'to contribute to the establishment of best available practice regarding impact categories, together with category indicators, and lists of concomitant characterization factors to be used in life cycle impact assessment' (see WIA2 Background Document, Udo de Haes et al., 1999). The main objective of the Human Toxicity Task Group was to identify and discuss the suitability of toxicological impact measures for human health for use in characterization in LCIA.

Toxicological characterization factors for human health are calculated by taking into account the time-integrated fate, exposure of a unit mass of chemical released into the environment (including, in many cases, the size of the exposed population), toxicological potency (a quantitative measure related to the dose–response of a chemical, such as the LOEL – the Lowest Observable Effect Level in a test) and toxicological severity (a measure or description, qualitative or quantitative, of the effect incurred, such as bladder cancer or skin irritation). These stages are illustrated in Figure 1. The Human Toxicity Group, hence this paper, addressed current and developing practice in the areas of toxicological potency and severity for LCIA. With minor exceptions such as the consideration of exposed population characteristics and size, fate and exposure are addressed separately by another working group (Hertwich et al. 2001).

Within LCIA, the assessment of effects related to the human toxicity impact category are focused on effects resulting from direct exposure to chemicals. Health effects caused by other agents, or by other mechanisms of action, are either not clearly allocated to one of the impact categories suggested e.g. in the SETAC WIA-2 background document (Udo de Haes et al., 1999) (e.g. impacts from radiation, fine particles, from noise), or they are covered by other impact categories (e.g. health effects due to increased tropospheric ozone concentrations). While the mechanism of exposure in these cases might differ from that of toxic chemicals, the resultant effects on human health are best described using

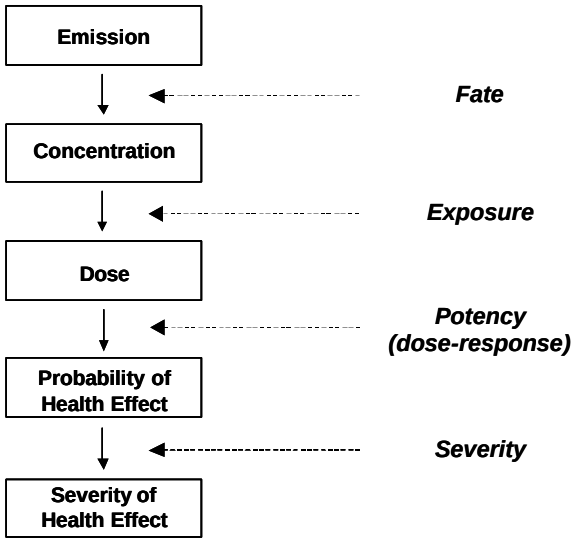


Figure 1: Illustrative outline of stages for the calculation of characterization factors for human health

comparable indicators. Therefore we make an attempt in this paper to extend the human toxicity impact category to a human health category by taking into account effects from fine particles, tropospheric ozone, and radiation. In the case of tropospheric ozone, the photochemical ozone creation potential (POCP), which primarily reflects fate and exposure, is discussed in detail in the related SETAC position paper by Potting et al. (2001). Health effects due to stratospheric ozone depletion and global warming are not addressed here, but the indicators discussed can in principle be equally applied for these impact categories.

Following the recommendations of the WIA2 Background Document, one of the major challenges for the assessment of human health effects in the context of LCIA is to extend current indicators that are based on a substance's potency by providing information on the severity of the expected effect in the environment. Human health indicators are classified and presented here as toxicological potency-based indicators (reflecting the likelihood or probability of an effect, which is sometimes termed hazard) and severity-based indicators (reflecting both the likelihood and the consequences or resultant damage[1]). Taking severity into account is, theoretically, expected to increase the amount of information available to decision makers, hence to improve the basis of their decisions. This additional information is also expected to help improve subsequent weighting and valuation steps in LCA. Both qualitative categorization and quantitative scaling approaches are therefore discussed.

Severity indicators provide information that is sometimes considered environmentally more relevant (i.e. more directly linked to society's concerns), but the relationship to the environmental interventions can be more uncertain. However, both potency-based and severity-based indicators are considered as so-called endpoint related indicators.[2] For a given population, potency-based indicators provide a measure of the likelihood of people to be potentially affected by an emission. Severity-based indicators provide a measure that takes into account resultant hardships that may be experienced in terms of, for example, years of quality life lost due to death or injury. Severity-based factors therefore go a step further in specifying the effect that is of societal concern. Noting the conclusion of the SETAC/USEPA/CML Brighton Workshop (Bare et al. 2001) that indicators should be presented at different points in the environmental mechanism to provide different insights with differing types of uncertainty, it is expected that potency- and severity-based approaches will be used in a complementary way. The relative merits of each indicator basis are discussed in this paper, with the aid of selected criteria.

In section 2 we outline current practice in LCA. Sections 3 and 4 discuss the various approaches and related issues under the headings of potency and severity, respectively. An evaluation is presented in section 5, with concluding remarks in section 6.

[1] The term 'damage' is sometimes used to describe an *economic* damage resulting from an environmental impact, while we refer here to a *physical* damage. We adopt "severity" for precision and its current acceptance in the toxicological literature. For example, Murray et al. (1996) refer to the severity of disease.

[2] Factors can reflect measures at "midpoints" or "endpoints"; depending on whether they reflect differences at midpoints or endpoints in the environmental mechanism, or cause-effect chain (Bare et al. 2001).

2. Current practice in LCIA

A range of indicators are in current use. Eco-indicator 99 (Goedkoop et al., 1999) is one example of a tool in which both potency and severity are taken into account. The EPS-methodology uses a severity-based indicator where morbidity and nuisance[3] are then weighted by a willingness-to-pay (WTP) approach (Steen et al., 1999). Although not a LCA-methodology, the ExternE project (European Commission, 1999) also adopted severity-based indicators weighted by using willingness-to-pay data as an indication of individuals' preferences. Most other methodologies currently use potency-based indicators. Several methodologies for assessing toxicological effects to humans using potency-based indicators have been proposed by Guinée et al. (1996) (updated by Huijbregts et al., 2000), Jolliet and Crettaz (1996), Hauschild et al. (1997), and Hertwich (1999).

Available methodologies follow the framework presented by the first SETAC working group (Jolliet, 1996), i.e. that the impact score for each substance is presented as the product of an effect factor, a fate and exposure factor, and the total mass loading of the emissions (see also Figure 1). This framework is adapted from the principles of risk assessment.

The fate and exposure measure in LCIA is a predicted daily intake, i.e. a daily dose (ingested or inhaled). More recently, this has been expressed as an exposure efficiency or dose-fraction (e.g. fraction of mass released that is either inhaled or ingested). In line with the doctrines of LCA, the fate and exposure measures account for the time-integrated concentration of the substances in each environmental compartment and associated exposure related to factors such as inhalation and consumption rates (of vegetables, beef, milk and fish etc. associated with complex food webs). Dermal exposure is not addressed in most current approaches due to a lack of associated toxicological data for this route and the common opinion that it is often a relatively negligible pathway (which may not be true in all cases).

The toxicological potency measure in LCIA approaches is usually a slope factor based on risk per unit dose of a given effect for carcinogens and, either implicitly or explicitly, on the dose-response gradient between zero and a given measure for non-carcinogens. No threshold is generally assumed, or taken into account, and both gradient measures are usually on a linear scale. These 'no-threshold' and 'linear' assumptions eliminate the need to account for background concentrations at specific sites when estimating the marginal change in effect associated with a given emission. Crettaz et al. (2002a, b) summarize arguments in support of these assumptions. LCA is expected to continue to adopt such no-threshold, linear approaches, while complimentary methodologies such as risk assessment may address whether or not acceptable adverse risk levels are exceeded for specific emissions at specific sites.

The toxicological potency measure selected for a chemical may be a value derived from an extensive review of the available toxicological literature by an expert panel, as reflected in the derivation of regulatory measures such as the ADI by JECFA/WHO and the RfDs by US EPA, or derived from a survey of databases (RTECS, HSDB, etc.). In both cases, the potency is usually based on laboratory studies conducted on experimental animals and then extrapolated using factors to arrive at a relevant measure (for example, in some methodologies, acute data from tests on rodents are extrapolated to chronic measures for humans). Problems for LCA practitioners include inconsistency in the degree of

3 Nuisance is here understood as a mild form of nuisance that does not constantly irritate people. Visibility reduction, dirty surfaces or a moderate noise level is regarded as nuisance. (Steen et al., 1999)

conservatism adopted for extrapolations in and across regulatory applications and the availability of multiple measures for some compounds.

LCA usually does not permit the quantification of actual effects, primarily due to practices adopted in the inventory phase, but enables the characterization of the relative impact of emissions associated with a product's life cycle (Udo de Haes, 1996). The toxicological indicator of each substance emitted must be additive in order to aggregate the indicator results of the many different emissions occurring throughout a life cycle. If population is taken into account, when added, current potency indicators provide a count of the number of people affected by a given emission (if not, the risk of an effect to an individual). In current practice for potency-based indicators, these are then summed across the different emissions, noting that an individual in the population may be affected by more than one emission. Relative severity is not considered. Reflecting some extreme stances, the relevance of such potency-based indicators is therefore questioned (e.g. Owens, 1996, 1998).

The damage to human health of a chemical may be substantially different depending on whether the effect is, for example, a gastrointestinal inflammation lasting for a few days or weeks or it causes a severe foetal malformations. This is sometimes regarded as a limitation of current practice (Burke et al. 1996). Some practitioners have therefore adopted, or proposed, measures to take into account the relative severity of a chemical (European Commission 1999, Goedkoop and Spriensma 1999). The categorization of potency-based indicators and the so-called severity-based indicators account for both potency and severity, sometimes using epidemiological insights (Hofstetter 1998).

Different formats have been adopted to convey results to decision makers. In some methodologies the result is presented in the form of an equivalency factor. In the equivalency factor approach, the combined fate-exposure-potency factor of a substance is divided by that of a reference substance (e.g. 1,4-dichlorobenzene used by Guinée et al. (1996)). The final indicator value then reflects the result in terms of equivalents of the reference substance (e.g. the relative toxicological impacts associated with one life cycle compared to another in terms of 1,4-dichlorobenzene equivalents). Other methods, such as EDIP (Hauschild and Wenzel, 1997), avoid the use of a reference substance but reflect the results instead in terms of a "critical volume" approach. The critical volume is the volume of water, air or soil in which the pollutant must be diluted in order to not exceed a given potency (or severity) level. The choice between these approaches may have consequences on interpretation in the valuation and weighting phases.

In the next two sections, the merits and limitations associated with different potency and severity measures are discussed. For additional discussions that provide greater depth on some of the summarized issues the reader is advised to consult, for example, (Crettaz et al. 2002a, b; Olsen and Hauschild, 1998; Owens, 1996; Owens, 1998; Barnthouse et al., 1997; Udo de Haes, 1996; Jolliet, 1996; Burke et al., 1996).

3. Toxicological potency (dose-response)

We commonly use toxicological potency as an indicator for toxic effects, as a first step prior to considering severity or as an endpoint indicator in its own right. In principle, all chemical substances can

cause adverse effects on humans. In contrast to other impact categories, human toxicity therefore theoretically includes all substances (and emissions) and it includes many different toxicological effect mechanisms. The detailed mechanism of action is not however known for most substances.

There is a long tradition of using toxicological information, especially for regulatory purposes (e.g. authoritative approval of drugs, pesticides and other chemicals). For the detailed assessment of the toxicological effects of a substance to humans, knowledge of the following issues is desirable/necessary:

- Uptake, distribution, metabolism and excretion of the substance in the human organism (metabolism rates and pathways of the same substance can vary significantly between individuals, which is one parameter giving rise to differences in sensitivity)
- The effects of the substance (acute toxicity by inhalation, oral, or dermal exposure; irritation and sensitisation properties; systemic toxicity; carcinogenicity, genotoxicity, reproductive toxicity, neurotoxicity, immunotoxicity)
- Dose-response relationships
- The biological mechanisms by which the substance exerts its effect, noting that a substance may have several effects and, although it has been tested to describe one effect, it is not possible to draw parallels to other types of effects because different mechanisms may be involved.

Although a well-established scientific background for retrieving toxicological information and data exists, experimental toxicological information is only available for a small percentage of the marketed chemicals (see Table 1). In the absence of such data and for ethical reasons, tools are becoming more widely available to predict toxicological potency; but their scope and reliability often remain limited.

Most toxicological studies aim at deriving information that may be used to establish a virtually safe dose for regulatory purposes, such as an ADI (Allowable Daily Intake), below which no unacceptable risk of adverse effects is expected. The toxicological information will often be established through experiments, which are not without fundamental problems (NRC 1994). The experiments are usually conducted for chemicals in isolation using small groups of test animals. The purpose is to provide a qualitative understanding of the effect mechanism and a quantitative determination of the dose- response relationship for known effects considered hazardous or critical. Given the conditions of the experiments, often short term mortality studies using rodents, it is commonly necessary to extrapolate to a more relevant basis; namely humans. Given such insights, the relevance of the results in the context of human populations, with various levels of resistance, exposed to such chemicals as part of complex, often-interacting mixtures, is still widely debated.

Table 1: Availability of toxicity data for High Production Volume Substances (> 1000 t in EU). For all marketed chemicals it is estimated that only 5-10% are studied for acute toxicity and 1% for longer term toxicity such as cancer, reproductive toxicity etc. (Bro-Rasmussen et al., 1996). A study by US EPA reached similar conclusions regarding the data availability for High Production Volume chemicals (US EPA, 1998) as shown in the table.

Data type	Availability estimated by the European Chemical Bureau	Availability estimated by the US EPA

Acute toxicity	90 %	49 %
Subacute toxicity	53 %	-
Carcinogenicity	10 %	-
Mutagenicity	62 %	34 %
Fertility	20 %	23%
Teratogenicity	30 %	
Chronic toxicity	-	14 %
Acute ecotoxicity (fish or daphnia)	55 %	-
Short term toxicity (algae)	20-30 %	-
Toxicity to terrestrial organisms	5 %	-
Environmental fate	-	31 %

In the next two sections (non-carcinogens and carcinogens) we provide a more detailed discussion of the merits and limitations of currently available potency measures with an objective of identifying a path towards best-available practice in LCIA. Note that this distinction into non-carcinogens and carcinogens is rather historic in nature, as it may not reflect the relative severities of the chemicals or differences in how the potency (dose-response) measures should be addressed as discussed later.

3.1. Non-carcinogens

In traditional toxicological safety assessments the ultimate aim is to estimate a virtually safe dose, e.g. ADI (Acceptable Daily Intake used by JECFA, WHO), RfD (Reference Dose used by US EPA) etc. This is achieved by determining the critical effect and estimating the NOAEL (or Lowest Observed Adverse Effect Level, LOAEL) for this effect. The NOAEL is the highest dose that does not cause a statistically differentiable effect of interest in the test population studied, which is then often extrapolated to humans. The toxicologist's interpretation of the experimental data is crucial for the determination of the adverse effect. The designation of a given effect as adverse becomes increasingly complex as increasingly subtle effects are identified by more sophisticated techniques and assays (DeRosa et al., 1989).

The NOAEL (or LOAEL) can be divided by extrapolation factors to account for differences in sensitivity between human and animals, between humans (i.e. specifically sensitive individuals), and between short-term test periods and long-term exposure periods of the human populations. Furthermore, a modifying factor can be employed based on a judgment of the study quality and relevance (Barnes and Dourson, 1988). In essence, the derivation of virtually safe doses requires professional judgment and each individual toxicologist or panel of toxicologists develop their own judgment of principal studies, critical effects, extrapolation factors etc. Virtually safe doses developed by different institutions and the level of conservatism across chemicals are therefore not always similar, which pose a problem in LCIA.

In 1992, the US Society of Toxicology held a symposium addressing such issues in Quantitative Noncancer Risk Assessment (Beck et al., 1993). The basic thrusts of the symposium were:

1. How can mechanistic and other data be used on a case-by-case basis to avoid the use of default extrapolation (uncertainty/safety) factors.
    - The safety factors are arbitrarily set at 10. This means that the level of protection may differ from chemical to chemical; and that risk assessment and risk management are inappropriately combined (Baird et al., 1996).
2. How to incorporate the full set of experimental data into the determination of toxic potency

- The ADI is based on only one value and as such is dependent on the conditions of one particular experiment.
- Experiments involving fewer animals tend to produce larger NOAEL's and as a consequence may produce larger virtually safe doses.
- The slope of the dose-response curve plays little or no role in determining the NOAEL.

In the next three subsections we discuss problems associated with extrapolation, different measures adopted to calculate the potency measure in LCIA and the existence of thresholds.

Extrapolation

Toxicologists' traditional use of factors for extrapolation between species, extrapolation to sensitive individuals, and extrapolation from less-than-chronic studies, is a subject of considerable discussion (Pennington 2002, Baird et al. 1996, Dourson et al. 1996). For commonly termed safety factors, data are often divided by a safety factor of ten for each required extrapolation. However, it has been found that the real differences represented vary considerably between substances. For example, in many cases a factor of 3 may be adequate for the extrapolation from subchronic to chronic exposure, whereas inter-individual variability in susceptibility has been shown to be as high as 10,000 (Beck et al., 1993).

In addition to the difficulties of extrapolation, ADIs and RfDs are intended to provide a virtually safe dose. Test results are commonly extrapolated to "safe doses." This practice can result in bias for chemicals with few data, which is sometimes considered desirable in regulatory screening applications. As the need in LCA is a realistic effect-potential to be comparable with the other impact categories, Burke et al. (1996) argued that using a NOAEL directly without safety factors would be better for LCA purposes. However, the very limited data availability emerges as a significant drawback, because a reliable chronic NOAEL is only available for relatively few substances as illustrated in Table 1.

Extrapolation is still a widely accepted practice amongst toxicologists and is considered to remain necessary in LCA. To support this practice, best-estimate extrapolation factors can be calculated from empirical insights with associated uncertainty distributions (Jager et al., 1997; Pennington, 2002).

Potency measures: NO(A)EL vs. BMD vs. ED_{10}

As described earlier in this section (3.1), the NOAEL (No Observed Adverse Effect Level) is the highest dose that does not cause a statistically differentiable effect of interest in a tested population. In the USA, the Benchmark dose (BMD) is a progressing alternative measure, although not yet widely applied. The BMD is an estimate of the lower confidence limit of the dose that affects a small percentage of the population (e.g. 1, 5, or 10%) compared to the control group. The percentage chosen can depend on the severity of the critical effect (e.g GI inflammation 10% and teratogenic effects 1%). One of the goals in selecting a Benchmark Risk (BMR - the level of increased response that the benchmark dose represents) is to make it as small as practical without the BMD becoming too model dependent. The estimation is based on statistical modelling of the dose-response curve, which is continuous, whereas a NOAEL will always be one of the experimental doses and, thus, in part is chosen by the study investigators. The US EPA (1995) referred to three studies in which the NOAEL and BMD were compared for an array of data sets. In almost all cases, the BMD turned out to be smaller or similar to the NOAEL.

Crettaz (2000) and Crettaz et al. (2002a, b) adapted the Risk Assessment concept of BMD for LCIA,

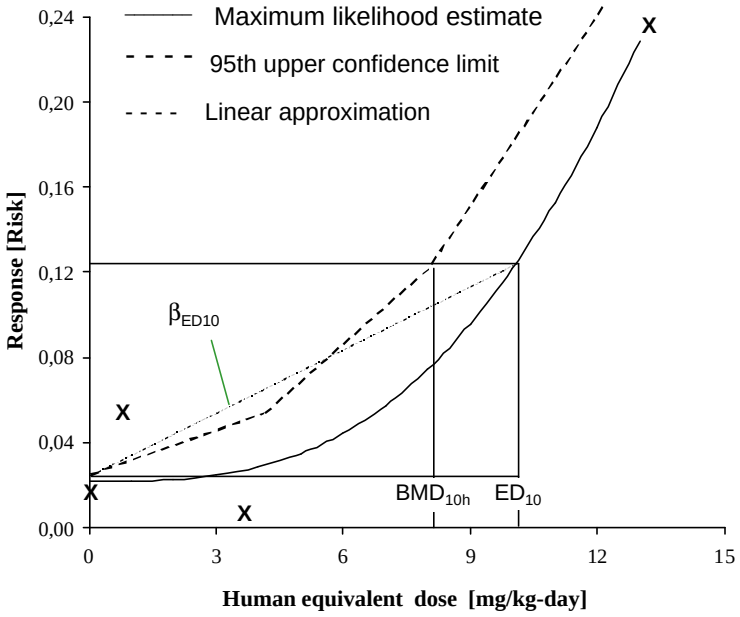
proposing to adopt the ED_{10} measure (subscripted with h for humans or a to denote animals). ED_{10} is the best estimate of the dose inducing a 10% added risk over background for humans (see Figure 2). This proposed ED_{10} approach differs from the US EPA's application of the BMD_{10} at two levels:

- The ED_{10} is considered instead of the BMD_{10} to obtain the best estimate of the risk rather than an upper bound. The lower confidence limit provides one estimate of the associated uncertainty range.

- While the US EPA proposes to use the benchmark dose to derive a reference dose (i.e. an estimate of daily oral exposure that is likely to be without an appreciable risk of deleterious effects during a lifetime), Crettaz et al. (2002a, b) instead use the ED_{10} to quantify the risk of toxic effects, assuming a linear dose-response curve without threshold ($\beta_{ED10}=0.1/ED_{10}$; risk per unit dose, see Figure 2).

The non-threshold assumption is considered justified by the growing recognition that "no evidence" does not necessarily mean "no effect" and that bioassays cannot give real insights on linearity or non linearity at low doses, which only depend on the extrapolation model adopted. In agreement, recent epidemiological studies have suggested that there are no safe levels for some compounds. This issue is discussed further in the next section.

The ED_{10} is highly correlated with the benchmark dose and to the more widely available NOAELs for animals (Crettaz, 2000; Crettaz et al. 2002a, b). Crettaz et al. (2002b) present ED_{10}s and corresponding β_{ED10} slope factors for over 600 chemicals. Given the high uncertainty, extrapolation of ED_{10} from the lethal dose data (e.g. LD_{50}) unfortunately cannot be considered to be reliable beyond preliminary screening (Crettaz et al. 2002a, b; Pennington, 2002; Crettaz, 2000).



95^{th} upper confidence limit
BMD_{10h}: Benchmark dose for humans
ED_{10h}: Effect dose for humans
β_{ED10}: Slope factor based on the ED_{10h}

Figure 2: Dose-response measure β_{ED10} for acephate (insecticide) predicted by fitting the multistage model of Crouch (1985) to the data (denoted X on the figure) observed in a mice bioassay, as reported in the Integrated Risk Information Service database (US EPA, 1998). (Crettaz et al. 2002a and b) Similar approaches are adopted to derive slope factors. The number of data are commonly limited and provide little insight into the true dose-response curve, especially at low doses, because of background risks.

Thresholds

Toxicologists argue that mechanistic threshold concentrations or doses may exist for human health effects for many substances, noting that statistically differentiable thresholds are observed for individual substances tested on small populations of carefully maintained test animals. Bioassays cannot provide insights into low dose responses (below say a risk of 10^{-2}) and, below acceptable risk thresholds (usually a risk of 10^{-4} to 10^{-6} or a measure based on the NOAEL for non-carcinogens), the extent of additive, synergistic or antagonistic effects remains unknown. In epidemiological studies it has commonly not been possible to establish the existence of mechanistic thresholds (e.g. European Commission, 1999).

In LCA, accounting for thresholds will require site-dependent background information and the consideration of interactions within complex mixtures. The derivation of such thresholds and accounting for them will long remain beyond the scope of LCA. A precautionary stance of no-thresholds is appropriate following the doctrines of the precautionary principle. LCA will continue to provide a powerful tool to identify areas for improvement and, possibly, to focus resources for further site-dependent investigations.

3.2. Carcinogens

At least for genotoxic carcinogens it is believed that there is no virtually safe dose because there is no mechanistic threshold for the carcinogenic effect, hence, up to now, associated substances have been addressed separately in traditional risk assessments. Known non-genotoxic carcinogenic effects, as well as necessary extrapolations for genotoxic effects, are treated analogously to non-carcinogens, as described in the previous section (3.1).

The risk that the substance causes cancer at different doses is estimated by modelling using bioassay data, e.g. based on the low-dose slope factor of a dose-response curve, extrapolated from data in the observable range. The term ‘slope factor’ used by the US EPA is based on a similar concept and describes the increased cancer risk from a lifetime exposure to an agent per mg substance intake per kg body weight (risk per unit dose per kg body weight). The World Health Organization (WHO, 1987) adopts a similar measure known as the unit lifetime risk or unit risk. The unit risk factor is an estimate of the probability that an average individual will develop cancer when continuously exposed to an agent at a concentration of 1µg/L in water, or 1µg/m^3 in air over the individual’s life (70 years).

There are various international and national bodies, including e.g. the WHO or the US EPA, that suggest unit risk factors and slope factors for a wide range of different substances. The IRIS database of the US EPA provides a quite comprehensive compilation of unit risk and slope factors (http://www.epa.gov/ngispgm3/iris/). Hofstetter (1998) and Crettaz et al. (2002a, b) provided a compilation of unit risk factors and slope factors from various sources.

As mentioned in section 2, methods currently applied in Life Cycle Impact Assessment (LCIA) for characterizing the carcinogenic effects are based upon the principles developed in Risk Assessment. These principles and their application in LCA have been reviewed by, for example, Crettaz et al. (2002a, b), Pennington (2002) and Crettaz (2000). Most methodologies, for example the Eco-Indicator 99 approach (Goedkoop et al, 1999; Hofstetter, 1998), adopt the low-dose slope factor q_1^* measure to quantify the risk of cancer. However, there are some drawbacks to their application in LCIA. Firstly, the dose-response assessment is based upon the extrapolation towards low dose using a mathematical model, most commonly the linear multistage model. Using such models is open to criticism, since associated extrapolations can lead to large differences in the projected risk at low doses depending on the model selected (Crettaz et al., 2002a, b; Crettaz, 2000). The high associated uncertainties of extrapolating the dose-response curve towards low doses are usually hidden.

The application of the Benchmark Dose-10% has recently been proposed (US EPA, 1996). Like non-carcinogens, Crettaz et al. (2002a, b) and Crettaz (2000) proposed the related ED_{10} measure for use in LCIA to provide a consistent basis for comparison. The effect dose ED_{10} is defined as the best estimate of the dose corresponding with a 10% risk over background. A linear dose-response curve without threshold is retained for low dose extrapolation ($\beta_{ED10}=0.1/ED_{10}$) in LCA.

Using the IRIS database, Crettaz et al. (2002a, b) demonstrated that β_{ED10} and q_1^* are strongly correlated. ED_{10}s are also strongly related to the US EPA's BMD_{10}. A correlation was similarly found between ED_{10} and the Toxic Dose 50 (TD_{50}; or ED_{50}) values reported in the Carcinogenic Potency Database (Gold and Zeiger, 1997). As a result, values of β_{ED10} were calculated for 600 substances (Crettaz et al., 2002a, b; Crettaz, 2000). No robust correlations with LD_{50} data (lethal dose data from short term studies resulting in 50% mortality within the study period) have been suggested in the literature.

3.3. Radiation

Although radiation effects in general are not considered as toxic effects, as a response to Udo de Heas et al. (1999) we suggest here to include radiation effects under the 'human toxicity' impact category in order to provide a harmonised conceptual framework for the assessment of different impacts on human health. Ionising radiation leads to an increased probability of cancer, so that indicators similar to those used for carcinogenic substances can be used.

The manifestation of the health effects after exposure to ionising radiation are governed by different biological mechanisms and have been classified into two categories: deterministic effects and stochastic effects. Deterministic effects occur above a threshold level of radiation exposure (approximately 1 Sievert), and the severity of the impact increases with increasing exposure. Below the threshold level of deterministic effects, one becomes concerned with stochastic effects. In this range of doses, an increase in dose increases the probability of an effect, but not the severity of the effect. In the field of LCA we are generally dealing with low doses that result in stochastic effects.

The calculation of expected occurrence of cancer or fatalities following radiation exposure is facilitated by mathematical models involving the age-specific baseline rates and a small number of regression parameters estimated from epidemiological data. Most information available for estimating the effects of exposure to ionising radiation comes from the follow-up study of the survivors of the atomic bomb

explosions at Hiroshima and Nagasaki. The International Commission on Radiological Protection in its ICRP 60 publication (ICRP, 1990) has recommended risk factors that establish a relationship between the exposure and the occurrence of fatal cancer, non-fatal cancer and hereditary effects. An operational model for inclusion of human health damages caused by radiation into life cycle impact assessment has been developed for use in Ecoindicator 99 by Frischknecht et al. (2000).

4. Severity

The International Life Sciences Institute (ILSI), Health and Environmental Sciences Institute (HESI) constituted an expert panel to give recommendations on a methodology for addressing toxicological impacts in LCA (Burke et al., 1996). As already discussed, one of their main reservations related to existing methodologies was the use of toxicity values that incorporate safety factors (e.g. the Reference Dose, RfD, used by the U.S.EPA or Acceptable Daily Intake, ADI, used by JECFA/WHO). The other main reservation was the disregard of the severity of the effects (Burke et al., 1996). The methodologies for assessing human toxicological impacts in LCA are sometimes criticized for not reflecting the severity of an effect, because they aggregate toxicological measures based only on the No Observed (Adverse) Effect Level (Burke et al., 1996; Jolliet, 1996; Owens, 1996), or similar. The procedure can provide a relative measure of the number of individuals affected, for example, but irritative substances are implicitly valued equal to substances having irreversible effects like foetal malformations. In an effort to overcome such limitations, both qualitative and quantitative methodologies have been proposed.

4.1. Qualitative approaches to account for severity

To better take into account the severity of different health effects, the International Life Sciences Institute (ILSI) panel proposed a classification of substances in three subcategories according to the severity of the related effects (Table 2). Jolliet (1996) proposed the use of similar subcategories, or if this is not possible, a classification into known mechanisms (e.g. acute toxicity, irritation, carcinogenicity, teratogenicity etc.). More recently, Owens (2000) has expanded on the ILSI proposal for sub-categorisation, testing the applicability of this proposal with USEPA-IRIS datasets. The ILSI panel approach is summarised here to exemplify some of the benefits and problems associated with

categorisation.

The ILSI-panel procedure has both scientific and subjective (i.e. "value-laden") components and requires input from experts because "informed valuation" is a critical part of the process, for example when classifying substances into subcategories. As mentioned earlier, also the scientific part includes professional judgment. The subcategories can be "weighted" in the characterisation/valuation step;

Table 2: Proposal for the definition of human toxicity subcategories according to the severity of effect (Burke et al., 1996).

Impact category: Human Toxicity		
Subcategory 1: Irreversible/life-shortening effects	Subcategory 2: Maybe reversible/maybe life-shortening	Subcategory 3: Generally reversible/ generally not life-shortening
Related endpoints (examples): Cancer Reproductive effects Teratogenic effects Acute fatal or acute severe and irreversible effects (i.e. fatal poisoning) Mutagenicity	*Related endpoints (examples):* Immunotoxicity Neurotoxicity Kidney damage Liver damage Heart disease Pulmonary disease (i.e. asthma)	*Related endpoints (examples):* Irritation Sensitization Reversible acute organ effects (i.e. GI inflammation)

subcategory 1 for instance by a factor 100, subcategory 2 by a factor 10 and subcategory 3 by a factor 1 (Burke et al., 1996). The procedure involves several other steps before reaching a toxicity and persistency equivalence. The main point of interest for discussion here is the classification step as a possible way of reflecting the difference in severity of toxic effects.

The three sub-categories each reflect a more homogeneous endpoint whose relevance is easier to interpret in terms of consequences than a single aggregated potency-based potential. The subcategories therefore provide a better input for decision making. However, the classification involves value judgement, as does the definition of which effect types should be included in each subcategory. Even the ILSI panel, had to note that neurotoxicity by some is ranked equally or more severe than cancer (Burke et al., 1996). Furthermore, the severity of effect may not be equal even within the same sub-category of effects. An example of this is cancer, as different cancer types have different survival probabilities and times.

When subcategories are introduced, it could be questioned whether the substance should only contribute to the subcategory of its critical effect or to all subcategories to which it contributes. It is highly uncertain that the substance is studied for all effects. Furthermore, there is a risk of double counting if different effects related to the same substance occur in several subcategories. The recommendation is to include only the most severe effect.

As illustrated in Table 1 and described in the previous section, the availability of toxicological data is very restricted and for many of the inventory items it may not be possible to find suitable data for the classification into effect-type subcategories. The classification into the subcategories proposed by the ILSI panel is feasible for those substances reviewed by US EPA and listed in IRIS, because a thorough evaluation of effects has been performed (Owens, 2000). Based on a newly proposed classification,

Owens (2000) tested the applicability of his proposal with the IRIS datasets for 2200 high production volume chemicals in an attempt to explore whether a relatively limited number of toxicity categories broken into cancer and non-cancer was at all feasible in regards 1) to classification and 2) compatibility and feasibility with the existing regulatory toxicity databases (and implicitly the large body of data in the literature, EU and OECD data bases, industry files, etc., since the same or similar bioassays are used). He found that all non-cancer endpoints are rather easily classifiable and that there is a good starting set for classifying into genotoxic and non-genotoxic carcinogens. But even in the IRIS database there is a wide variability among the data. However, those substances for which less valid and incomplete information has been found in RTECS (and partly HSDB) cannot be classified into one or the other subcategory due to lack of knowledge. For these substances it would be necessary to perform a more thorough literature search and evaluation of the toxicological properties of the substance if such data exists. It would therefore be of great value to generate a list of accepted NOAELs or ED10s (or other measures of toxicological potency) and associated endpoints, evaluated by toxicologists, for those substances most frequently encountered in LCA inventories, as also mentioned by the ILSI-panel.

4.2. Quantitative approaches to account for severity

The approach of quantifying human health effects on the endpoint level of the environmental mechanism, i.e. in terms of physical impacts like e.g. loss of life expectancy or cough days, is an attempt to increase the relevance of the indicators, and thus make them more useful for the interpretation and valuation of results. The assessment of health endpoints requires indicators which are appropriate to measure a change in the health status.

There is a long tradition in the use of severity oriented health indicators to help measure the health status of individuals or a society in the fields of health management and environmental economics. Rosser's often cited index of 'Quality Adjusted Life Years' (QALYs) (Rosser, 1987) is an early attempt of measuring an individual's well-being on a single score, which was used for decision support in the UK health system. Many more or less similar indicator schemes have been developed in the past, the most recent and well accepted one is the DALY concept (Disability Adjusted Life Years) developed by Murray and Lopez (1996), which is also supported by the WHO. Similar to the QALY-approach, the DALY concept translates non-fatal adverse health effects that can be classified according to a multi-dimensional scheme into a single score, and also establishes a trade off between premature death (expressed as years of life lost) and years lived disabled, i. e. the time span suffering from a negative health effect. The driving force behind the development of QALY- or DALY-type indicators was the increasing need of such indicators in health management to measure the health status of a given population.

There is also a growing interest in the approach of valuing health and environmental impacts in monetary units for policy oriented decision support, which is based on the theory of neo-classical welfare economics. In the US, a formal cost-benefit analysis is mandatory for the evaluation of various environmental policy measures, and also in Europe there is an increasing demand for using cost-benefit

analysis to justify new environmental regulation. The consideration of health and environmental impacts within a cost-benefit analysis requires the quantification of health and environmental impacts as far as possible on the endpoint level to facilitate a subsequent valuation. Fortunately, the developments in the fields of health management and environmental economics both led to comparable health indicators, in particular the Years of Life Lost (YOLL or YLL) is a key indicator used in both fields. Hofstetter (1998) introduced the use of the DALY concept in the LCA community. This is adopted in the Eco-indicator '99 methodology (Goedkoop and Spriensma, 1999) and by Crettaz et al. (2002a, b).

4.2.1. Fatal effects – the 'Years of Life Lost' (YOLL) indicator

An appropriate indicator to measure an increased mortality risk on the endpoint level seems to be the 'Years of Life Lost' (YOLL) indicator, which measures the reduction in life expectancy resulting from an increased level of exposure to pollutants in the environment. There is some discussion on the fact that the YOLL-concept, as it measures the loss of life expectancy resulting from a fatal event rather than the 'death' per se, puts a higher weight on the premature death of e.g. a 40 year old person than on the premature death of a 70 year old person (because the lost life expectancy is higher). Some people argue that the death as such is what matters, and that we should not a priori give a lower weight to the premature death of an old person. However, we know that the physical effect resulting from e.g. an exposure to a chemical is the reduction of life expectancy, as the probability of death is equal to one for any individual. Therefore we consider the 'Years of Life Lost' as an appropriate indicator on the damage level that can be quantified on the basis of natural science.

It should be noted, however, that at least in the economic literature the importance of the loss of life expectancy for valuation is controversial. Although the approach of putting a value on a life year is increasingly used in environmental economics, a study by Rowlatt et al. (1998) for the UK Department of Environment, Transport and the Regions and the Department of Trade and Industry e.g. strongly suggest to use a context specific Value of Statistical Life (i.e. different Values of Statistical Life for e.g. road safety and in the air pollution context) rather than a Value of Life Year for the valuation of mortality risks from air pollution. Rowlatt et al. (1998) argue that people's willingness to pay (WTP) to reduce mortality risks depends upon a great deal more than life span. The length of expected future life span is undoubtedly one factor for determining people's WTP to reduce the risk of premature death. It appears however to be only one of many factors, and one which over much of people's life is far from the dominant factor in determining how their WTP to reduce this risk changes with age. For the same reasons Rowlatt et al. suggest that the QALY indicator is better suited to the comparison of morbidity impacts than it is to the handling of risks of mortality (the same applies to the DALY indicator).

From our point of view this criticism is valid, and important for our discussion, as the health indicators to be used in LCIA should as far as possible reflect society's concern towards the effect at stake. However, with regard to the open and unresolved discussion on the valuation of mortality risk, the loss of life expectancy from our point of view still is the most sensible natural science based indicator for the quantification of increased mortality risk. Both the Years of Life Loss (YOLL) and the DALY indicator require the quantification of the loss of life expectancy.

4.2.2. Non-fatal effects

As mentioned above, we are facing a very large number of different non-fatal adverse health effects, and there does not exist any 'natural science based' indicator that allows the aggregation of different

endpoints to a single score. A set of morbidity endpoints linked to air pollutants that can be quantified by using dose-response functions was derived from a review of the recent epidemiological literature in the ExternE project (European Commission, 1999). It is obvious that this list of endpoints is not comprehensive, and it might be criticised that it reflects what is quantifiable rather than what is relevant for decision making. Although this is true in principal, we strongly believe that the underlying epidemiological studies have addressed health endpoints that are of direct social concern. So, we suggest as a pragmatic approach to assume that the list of morbidity endpoints is incomplete, but provides a reasonable approximation of the most important effects known today which are of direct social concern.

From a scientific perspective we are required to quantify and report results for every individual health endpoint. However, this inflation of subcategory-indicators is not manageable in an LCA-study, so there is a strong need to represent the various non-fatal health effects by using a single indicator. There exist a large scientific literature on the valuation of different health effects, which is used in national and international policy making, and thus might be used also as a basis for aggregation in LCIA. As it is supported by the World Health Organisation, the DALY concept would be the most appropriate one to be recommended as 'best available practice'. A problem might be that the DALY scheme up to now does not provide weighting factors for many of the health effects resulting from increased exposure to chemicals that we are mainly interested in LCA.

A weighting between some of the relevant health endpoints can also be derived from the economic valuation literature. The ExternE study recommends monetary values that are mainly based on recent contingent valuation studies in Europe and the US for a wide range of morbidity endpoints (European Commission, 1999). However, although ExternE results are currently used in policy oriented decision support, there is no international body that has authorised these values. From a comparison of weights allocated to different health endpoints it seems that the monetary valuation studies put a lower weight on the non-fatal effects compared to the risk of death than the DALY approach.

4.3. Availability of data to address expected severity

Carcinogenic severity data: The assessment of the carcinogenic potency of substances was discussed already in section 3.2. The operationalisation of the YOLL indicators requires quantitative information on the actual increase in cancer risk resulting from an increased exposure to a given substance, and on the expected loss of life expectancy per case of fatal cancer. Dose-response assessment involves describing the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury or disease. Data are derived from animal studies or, less frequently, from studies in exposed human populations.

For many recognised carcinogens, the target tissue and thus the type of cancer that is expected to develop is known. Hofstetter's review (Hofstetter, 1998) of studies quantifying the survival rate and the respective loss of life expectancy for different cancer types suggests that different cancer types result in about 15 to 20 years of life lost per fatal cancer, which is consistent with findings from e.g. the ExternE study or from the field of radiation protection (e.g. Erhardt et al., 1995). Together with a slope factor or unit risk factor, which give the probability of effect, the information on the respective loss of life expectancy per case of fatal cancer can be used to estimate the Years of Life Lost per unit change in the concentration of a carcinogenic substance.

The International Commission on Radiological Protection in its ICRP 60 publication (ICRP, 1990) has recommended risk factors that establish a relationship between the exposure (collective dose) and the occurrence of fatal cancers, non-fatal cancers, and hereditary effects. As there are estimates on the loss of life expectancy for different fatal types of cancer, these risk factors can be used to calculate the Years of Life Lost, the number of non-fatal cancers, and the number of hereditary effects per unit increase in collective dose.

Non-carcinogenic severity data: The assessment of the non-carcinogenic potency of substances was discussed already in section 3.1. There are only relatively few non-carcinogenic substances for which it is currently possible to link the biological mechanism to a specific effect in humans, although the type of effect related to the potency measurements is reported in animal tests. Crettaz (2000) therefore proposed a preliminary approach in which DALYs are assigned to qualitative categories such as those described in section 4.1 above. There are, however, a large number of epidemiological studies that have analysed the correlation between various health endpoints and the concentration of 'classical' air pollutants like particles, SO_2, and ozone.

Results from epidemiological studies were used to derive dose-response functions, which allow the quantification of a wide range of health effects including both mortality and morbidity impacts (European Commission, 1999; Hofstetter, 1998). Taking into account the age specific death rate within a given population, the increase in mortality risk observed in the epidemiological studies can be translated into Years of Life Lost per unit change in concentration levels.

There is substantial epidemiological evidence of adverse acute health effects of particulate air pollution; and strong, but much less widespread, epidemiological evidence of chronic health effects (Hurley et al., 1999). The particles of main interest come from two principal sources: direct emissions from combustion processes, and the formation of secondary particles (sulphate aerosols and nitrate aerosols, from the emission of gaseous SO_2, NO_X, and NH_3). Based on a thorough literature review, the ExternE study (European Commission, 1999) provided a set of dose-response functions for the quantification of fatal and non-fatal health endpoints related to exposure to fine particles, SO_2, NO_X, and ozone.

Although causality of acute health effects is somewhat accepted, and that of chronic health effects quite widely accepted, there is no well-established mechanism of action of particulate air pollution. Epidemiological studies so far analysed the relation between the mass of fine particles and various health effects. Remaining open questions are to which extent the chemical composition of particulate matter influences the magnitude of its effect, and what is the influence of particle size on the ability of particles to induce effects (see e.g. Harrison and Yin, 2000). Correspondingly, there is little strong evidence on the relative effect of various kinds of inhalable particles. There is however some evidence, and strong conjecture, that (per unit mass ambient concentration) the relatively fine fractions ($PM_{2.5}$, sulphates) are associated with greater risks than PM_{10} generally. It may also be that the toxicity of particles is greater according to their acidity, and less according to their solubility. Others regard particulates as indicators of overall pollution, rather than the sole cause of the associated impacts. The latter point implies that existing potency estimates for particulate matter may significantly exaggerate their true importance.

As the ambient air concentration of SO_2 and fine particles (which include sulphates and nitrates, among other substances) are often strongly correlated, for example, it is difficult in epidemiological studies to separate out the effect of the individual pollutants. Results available from epidemiological studies in the early 90^{ies} were interpreted in a way that the role of particles was more fundamental than that of SO_2 in these studies. However, a re-analysis of data from some US cities, sponsored by the US Health Effects Institute (HEI), together with new findings from the European APHEA studies (Air Pollution and Health: a European Approach), strengthened the case for an association between daily ambient SO_2 and acute health effects.

The principal epidemiological studies linking ambient concentrations of ozone with acute health effects have been carried out on the West Coast of the USA and in North-East USA/South-East Canada, and there are some recent data available from the APHEA study cities. Results of these studies provide substantial evidence of the acute health effects of ambient ozone.

Relatively few epidemiological studies report exposure-response relationships linking ambient NO_X with mortality or morbidity. In those that do, particles are generally also implicated, and there is some evidence that the apparent NO_2-effect is best understood not as causal, but as NO_2 being a surrogate for some mixture of (traffic related) pollution. However, NO_X is a precursor for the formation of ozone and nitrate aerosols, so that an effect on health via secondary pollutants can also be considered.

5. Evaluation of human toxicity indicators

In this section, the health indicators discussed in sections 2, 3 and 4 are assessed against a set of criteria to help identify the most appropriate indicators. The criteria were specified by the WIA-2 working groups.

Scientific validity and reliability:

Procedures of establishing, for example, Acceptable Daily Intake (ADI) values on the basis of NOAEL are scientifically accepted, although new approaches such as the benchmark dose (BMD) are emerging with adaptations for LCA. Uncertainty can be addressed quantitatively. Dose effect curves from animal studies and epidemiological studies in general provide confidence intervals. Similarly, probabilistic extrapolation factors can be adopted. The overall uncertainty of the indicator value also depends on the uncertainty linked to the fate and exposure modelling. There is however, not a common effect mechanism or mode of action, between different effect types and even within effect types. The degree of additivity is therefore sometimes questioned, but at a minimum provides an indicator or a score (somewhat related to a count of the number of cases in a population).

There is a still unresolved debate on the existence, or ability to measure thresholds and the extrapolation of the dose-effect curve towards low doses, particularly for non-carcinogens. Several scientific bodies have concluded that there is no scientific basis for assuming a threshold for genotoxic carcinogens, and in general a linear extrapolation of the dose-response curve (which might overestimate the effect) towards zero is recommended.

Dose-effect models exist for the assessment of physical health effects (often in the form of slope and unit risk factors) for a number of organic and inorganic substances and for ionising radiation that are adopted

or recommended by international or national authorities (e.g. WHO, US EPA), so that we can assume a sufficient general acceptance of the approach.

Although the valuation of increased mortality risk based on the loss of life expectancy is still partly controversially discussed in the literature, it is gaining growing acceptance, and the Years of Life Lost indicator is commonly used to measure increased mortality risk. There exist different approaches for the aggregation of non-fatal health effects to a single indicator. The selection of a specific approach is a value choice, rather than an issue of scientific validity, and up to now there is no consensus on which is the most appropriate one.

The use of indicators that account for severity requires the quantification of health effects resulting from an increase of exposure to a given substance. Most of the available dose effect models that link a change in ambient concentration level of a pollutant to a health effect are based on epidemiological studies and on animal studies. In most cases the actual mechanism that leads to the negative effect is not fully understood, so that the dose-effect model is based on a statistical association, which in case of biological plausibility is interpreted as causal. In spite of remaining uncertainties, this procedure can be considered as science based in the sense of ISO.

The use of the Years of Life Lost (YOLL) indicator is well established in some scientific and policy oriented areas. Reliable and widely-accepted science-based models exist (although uncertainties might be significant) for the quantification of YOLLs from different substances and for radiation. Although the reduction in life expectancy expressed as years of life lost is a 'physical' measure, the use of the YOLL indicator for aggregation includes a strong value choice, namely the assumption of equal value for any life year, irrespective of the affected person. While this view is not without controversy (see discussion above), we consider it as sufficiently accepted by society, so that it is justified within LCA. However, we note that YOLLs can still only be quantified for a limited number of chemicals using epidemiological data.

In contrast to mortality, the treatment of non-fatal effects is much more problematic. It is obvious that an aggregation of non-fatal health endpoints is mandatory to achieve operational indicators, but this aggregation requires value choices. An aggregation scheme authorised by an international body (like the DALY concept supported by the WHO) is desirable. Different approaches for weighting and aggregation currently discussed in the literature lead to different results. The future LCIA activities planned under the UNEP/SETAC umbrella might lead to a consensus on weighting factors for non-fatal health effects or a decision not to use them.

Based on the concept of risk assessment, the assessment of health effects in some LCA-studies is focused on the potential risk to a hypothetical individual, while the estimation of cumulated impacts that are expected to occur within an exposed population may be more appropriate in LCA. Small individual risks summed up over a large population might result in unacceptable large total impact, while a small collective risk might include an unacceptable high risk to the most exposed individuals. The choice between a measure of either individual risk or collective (population) risk is certainly a value choice that can affect the outcome of an LCA-study. Both individual and/or collective risk might be relevant in a specific decision context. However, assuming that current legislation helps to prevent non-acceptable risks to the most exposed individual at individual sites and from specific emissions, environmental

policy is increasingly concerned with the reduction of collective risks. We therefore conclude that the consideration of collective risk in LCIA will be of increasing importance.

Transparency and reproducibility:

The interpretation of results from animal studies might be somewhat different between professionals. Furthermore, the use of safety factors requires professional judgement. Consequently, virtually safe doses from various institutions may differ. It is therefore recommended to establish a single set of virtually safe doses, or similar potency measures such as ED_{10}s for use in LCA. These calculations can be made transparent, as demonstrated by the derivation of RfDs and RfCs by US EPA expert panels (all relevant information is published in IRIS).

The estimation of YOLLs and non-fatal effects depends on dose-effect models published in the literature or in relevant toxicity database systems. In particular risk factors for carcinogens are recommended by various organizations, and they partly differ between sources. As with potency, available data has to be reviewed, and a single set of factors should be recommended.

The consideration of severity can require some modelling linked to fate and exposure modelling – in particular the estimation of site dependent actual impacts – but this does not necessarily mean that the process cannot be presented in a transparent way.

Comprehensiveness and sophistication:

An indicator based on a virtually safe dose implies a perception that adverse effects from chemicals are unwanted. It provides a highly relevant measure of each individual chemical's potential to cause an effect on humans. Although based on risk assessment principles, it does not provide a measure of the risk.[4] The actual effect from environmental chemicals to humans in terms of morbidity and mortality is, however, quite difficult to interpret, but this is mostly due do insufficient exposure information.

Severity oriented indicators aim at describing the physical impacts that are expected to occur within an exposed group of persons: a measure often assumed to be the endpoint of the cause-effect chain (or environmental mechanism) for toxicological impacts. Both qualitative and quantitative approaches to accounting for severity are assumed to facilitate improved interpretation of results. To help avoid misleading conclusions associated with high uncertainties, however, it is currently recommended that results are presented with and without severity insights. Practitioners and decision makers should also be aware of the implications of the choice between individual versus population based-effect measures.

[4] Some practitioners consider that it provides an estimate of the time-integrated risk associated with a given functional unit (basis: time-integrated exposure combined with a linear dose-response gradient yields time integrated risk of an effect).

Dose-effect models in general give information on the change of the incidence rate of a specific effect as a function of the concentration level. The resulting effect therefore depends on the background incidence rate (e.g. mortality rate), which is influenced by many other parameters (e.g. lifestyle), and might differ between countries or regions. The provision of the relevant country specific data in general is very resource intensive. It is often assumed, in the absence of alternative insights, that the error introduced by using a constant risk factor is relatively small compared to other uncertainties.

Fate and exposure might be strongly influenced by local conditions (e. g. meteorology, population distribution). Models currently available to quantify health impacts at the endpoint level are mostly operated in a site dependent way. Results can be stepwise generalised (e.g. damage factors on the country level, continental level, global level; see discussion in (Hertwich et al., 2001)).

There might be a significant time period between the release of a substance and the negative health effect because of a latency time (e. g. cancer; several years) or long living radioactive decay products (several thousand years). For the impact assessment phase, we strongly recommend to present physical impacts without discounting. If discounting is required in the interpretation phase of LCA, the impact assessment phase needs to provide information on the time distribution of effects.

Although there is still partly controversial discussion on the shape of dose-effect curves at low doses and on the existence, or ability to measure, thresholds for most of the effects discussed above, several scientific bodies have concluded that there is no scientific basis for assuming such thresholds or no-effect levels for genotoxic carcinogens, ionising radiation, fine particulates and ozone. Arguments have similarly been proposed for non-carcinogens, citing that LCA should take residual risks below acceptable adverse effect thresholds into account. The linear extrapolation of the dose-response curve towards zero provides the most straightforward approach to the estimation of low-doses; noting that neither the shape of the low dose-response curve nor the existence of mechanistic thresholds can be determined in most bioassay studies.

In the case of linear dose-effect functions without threshold there is basically no difference between an average and a marginal analysis for the effect assessment. However, the formation of secondary pollutants (e.g. ozone) might strongly depend on background conditions, so that the difference between marginal and average analysis mainly affects the exposure modelling.

Relevance to the decision context:

The degree of additivity and the relevance of potency-based indicators is sometimes questioned. We note, however, that potency-based indicators can provide insights into the time-integrated risk of an emission associated with a functional unit. Following the principles of risk analysis, such measures can be added. These measures will not differentiate between severities of the associated risks. Lacking such a relevance, added potency-based measures should be interpreted with caution and may be misleading.

The distinction amongst chemicals in terms of severity may improve the information presented to decision makers, although practitioners have noted the need to provide potency- and severity-based factors in parallel. The YOLL is a ‘physical’ measure and allows the aggregation of different types of increased mortality risk from different substances, which however implies a value choice. Quantitative severity oriented indicators such as DALYs or QALYs provide one approach to compare across impact

categories taking morbidity into account. Qualitative approaches, such as the categorization of potency-based indicators, add information to the decision making process. The future LCIA activities planned under the UNEP/SETAC umbrella might lead to a consensus on weighting factors for non-fatal health effects or a decision to use one of the alternatives.

It is proposed to follow a three-step procedure depending on how valued information is desirable for decision making:

- Use a potency-based toxicity indicator, similar to current practice. This could for example be the dose-response slope derived from ED_{10} to bring together current practice for non-carcinogens and for carcinogens. These indicators do not provide information on the severity of the effects.
- If information on the severity is desirable, divide into subcategories based on the critical effect of the substance.
- Calculate severity-based indicators such as YOLLs and DALYs.

Feasibility:

There is a severe lack of toxicological data. It is therefore not possible to estimate a potency measure for all substances in a product life cycle, particularly for chemicals that are not yet of interest to an environmental agency. However, for most chemicals recognised as being severly hazardous, we are well informed about their toxicological properties.

We note that researchers such as Crettaz et al. (2002a, b) have compiled slope factors suitable for use in LCA, for over 600 carcinogens and over 400 non-carcinogens. Nevertheless, methodologies are required to now expand beyond such data sets. Estimation tools such as quantitative structure activity relationships (QSARs) and extrapolations from more readily available acute toxicity data may prove useful, although being suitable only for initial screening LCA studies due to high uncertainties.

The estimation of actual impacts (e.g. YOLLs in the actually exposed population) requires information on the spatial distribution of both the change in concentration and the population, which is not generally available. Specific models that provide this information can be used to produce damage factors, but such models currently do not cover all the relevant substances, and they are available only for selected regions.

In general, the effect models used to quantify severity oriented health indicators require ambient concentration data as an input from fate and exposure modeling. Severity oriented indicators can be used in two different ways:

- to calculate potential impacts within a predefined standard population (expressed e.g. as YOLLs or DALYs per person per unit change in concentration level), or
- to calculate actual impacts in absolute terms (e.g. YOLLs or DALYs per unit change in concentration level).

In the first case, severity oriented indicators are used in a way similar to potency based indicators. To assess actual impacts in absolute terms, we need to link the concentration data to data on the exposed population, which is a significant extension of current LCIA practice. The models currently used for fate and exposure modelling in LCIA in general do not provide the level of spatial resolution that is required

to consider site dependent exposure. However, models that have been developed for other purposes can be used to derive site dependent impact factors on different levels of spatial resolution (see e.g. Krewitt et al., 2001; Potting et al., 2000). In the field of ionizing radiation, site dependent impact factors have been derived for different source types (e.g. uranium mining, power plant, reprocessing plant) for representative sites by using complex models (UNSCEAR, 1993). However, the models that are designed to quantify actual health impacts by taking into account site dependent conditions up to now do not cover the wide range of substances commonly addressed in LCA. This issue is discussed in more detail in the corresponding paper of the SETAC WIA2 working group on fate and exposure (Hertwich et al., 2001).

Table 3-a: Summary review of different human health indicators with respect to their use in calculating characterization factors in LCIA – potency based indicators

Type of indicator	Key Advantages	Key Issues	LCIA application
Regulatory-based dose-response potency measures, such as ADIs, RFDs, RFCs	Widely adopted basis for site-dependent risk assessment to ensure regulatory compliance.	Inconsistent levels of conservatism, reflection of politically acceptable adverse effect risk levels rather than low-dose risk response measures.	(Hertwich, 1999), (Huijbregts et al., 2000), (Goedkopp and Spriensma, 1999), partly used by (Hauschild et al., 1997)
Slope factors based on benchmark doses, such as β_{ED10}	Introduced to provide a consistent basis for the derivation of low-dose risk response measures for carcinogens and non-carcinogens from a measure in the observable range.	Not currently widely adopted by regulatory agencies for risk assessment. While implicit in most measures for non-carcinogenic effects in LCA, adopting low-dose response curves for non-carcinogens remains somewhat debated.	(Crettaz et al., 2002a, b), suggesting values for approximately 600 carcinogens and 400 non-carcinogens.
Acute toxicity data, such as LD_{50}s and LC_{50}s	Widely available data.	Relevance of acute data when calculating time-integrated exposures to populations is poor and the relative acute to chronic importance is unlikely to be consistent across chemical emissions.	Partly used in (Hauschild et al., 1997). Extrapolations from acute to chronic data are widely adopted.

Table 3-b: Summary review of different human health indicators with respect to their use calculating characterization factors in LCIA – severity based indicators

Type of indicators	Key Advantages	Key Issues	LCIA application
Qualitative indicators			
ILSI classification: Health endpoints allocated to 3 categories according to reversibility and life-shortening of effect. Classification based on panel procedure (Burke et al., 1996)	The three categories represent a somewhat homogeneous group of health effects with different levels of severity. Provides additional information for decision support.	Allocation to categories might be controversial. The use of three categories allows rough severity ranking only. Weighting between categories currently requires value judgement.	Demonstrated by Owens (2000) and adopted by Crettaz et al. (2002b), who proposed an initial hybrid use of the categories with assigned DALYs.
Quantitative indicators			
Disability Adjusted Life Years (DALY), based on (Murray and Lopez, 1996), supported by WHO, World Bank	Allows aggregation of any health effects (mortality and morbidity) on a single cardinal scale.	No final consensus on weighting factors for different health effects. Different approaches (e.g. panels, willingness-to-pay) partly lead to different weights. Quantification of DALYs may not be possible for all relevant substances, particularly where effects are unknown when exposed to environmental mixtures .	(Hofstetter, 1998), Eco-indicator '99 (Goedkopp and Spriensma, 1999); (Crettaz et al., 2002a, b), who suggest preliminary defaults.
Quality Adjusted Life Years (QALY) (e.g. Rosser, 1987)	(similar to DALY)	(similar to DALY)	not currently used in LCIA but adopted in some comparative risk assessments.
Years Of Life Lost (YOLL) (also included in DALY & QALY calculations)	Allows aggregation of different mortality effects (different reduction of life expectancy) on a single cardinal scale based on a physical measure.	Giving the same value to any life year is a value choice that might not be commonly shared. Does not cover non-fatal effects. Quantification of YOLLs may not be possible for all relevant substances, as with DALYs.	key indicator in ExternE-type applications (European Commission, 1999)

6. Conclusions and recommendations

A main driving force for the further development of human toxicity indicators for life cycle impact assessment is the desire to improve the environmental relevance of the indicators, to decrease uncertainty, and to increase the number of substances that can be covered. In turn, the indicators are then more useful for valuation and weighting, and to address impacts from substances that are currently not well covered (e.g. radiation, fine particles). The approach of grouping different health effects that are quantified by using a toxicological potency based indicator to different health sub-categories can be seen as a potential step forward, as it may allow differentiation between different levels of severity. We suggest here to delve further into the feasibility and relevance of using such qualitative approaches to account for severity. The allocation of the different effects to categories leaves some practitioners with the question of how to derive weighting factors across the categories. There is currently no consensus on such weighting in the literature. DALYs, QALYs or monetary measures could be a possibility of quantitatively taking severity into account.

The use of severity-based indicators that describe the expected health effect in physical units is considered as a sensible way of further increasing the environmental relevance of the indicator value. In the case of mortality effects, the Years of Life Lost (YOLL) indicator is a natural science based indicator that allows the aggregation of different types of mechanisms from different substances into a single physical indicator. As the YOLL indicator is used in the field of health management and environmental economics, we feel that there is a good basis for its use in LCIA. It seems that the YOLL indicator can be quantified for a reasonable, but not yet sufficient number of substances.

The DALY- or QALY-type indicators that are currently used by some national and international organisations, provide a theoretically consistent framework for the aggregation of ‘all’ health effects (including mortality – measured as YOLL – and morbidity effects). However, the weighting of different health endpoints on a cardinal scale is a prerequisite for using DALY/QALY-type indicators, and this explicitly includes value choices. Current weighting schemes for mortality and morbidity endpoints do not lead to similar results, so that an internationally accepted and ‘authorised’ weighting scheme is desirable before suggesting DALY/QALY-type indicators as best practice for LCIA. It might be discussed to which extent the YOLL indicator (which is operational already today in many cases) shall be used only as part of a DALY/QALY-type indicator which combines fatal and non-fatal effects, or whether it can be used as an independent indicator (which people might interpret as ‘omitting’ non-fatal effects).

It was beyond the scope of the WIA-2 human toxicity subgroup to analyse in detail the tradeoffs between the use of a more sophisticated method on a perhaps limited subset of chemicals in an LCA versus the use of a less sophisticated approach that includes the majority of chemicals in an LCA. The decision towards a more or less sophisticated method will certainly depend on the context of the LCA study. Specific case studies like those carried out under the ongoing OMNIITOX project funded by the European Commission (http://www.omniitox.net) will provide insights about the usefulness of either approach for a range of different applications.

As a conclusion on the methodology we recommend a stepwise approach, which might be applied according to the objectives of the respective study, and the resources available. Step (1) is mandatory, while steps (2) to (4) are considered as complementary.

1) Use a potency-based toxicity indicator for the relative weighting between substances, similar to current practice. If desirable for decision making, differentiate between subcategories to reflect the different level of severity. Potency-indicators for substances like fine particles or radiation can be derived from published risk factors. Existing data sets for potency measures such as the ED_{10} which already now cover up to 1000 chemicals should be reviewed by experts, taking into account best-estimate extrapolation factors with confidence intervals, and associated critical effect information suitable for subsequent categorisation. The use of a sole peer-reviewed database will help to provide consistency within LCA and will be a valuable resource for other types of comparative assessment applications.
2) Calculate the YOLL indicator as far as possible for relative weighting between substances. This is only sensible if the quantification of YOLLs is possible for the key substances of the analysed processes in the LCA study. Check for changes in the resulting score compared to step (1), and – if applicable – discuss implications. If there is not sufficient information available to quantify YOLLs for all the relevant key substances, then we suggest to only use potency based indicators.
3) Calculate the DALY/QALY indicators for relative weighting between substances, as far as possible. As in the case of YOLLs, this is only sensible if quantification is possible for the key substances. Check for changes in the resulting score compared to step (1), and – if applicable – discuss implications.
4) If desirable according to the objectives of the study, and if information from the fate and exposure modelling is available, use endpoint indicators (YOLL and DALYS/QALY) to estimate health effects that take into account site dependent characteristics (e.g. total exposed population).

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